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DOCKET NO.: ISIS0231-100 (ISIS-3455)**SEP 23 2005****PATENT****IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

**Inventors: Cowser, Baker, McNeil, Freier, Sasmor, Brooks, Ohashi, Wyatt, Borchers, and
Vickers**

Serial No.: 09/295,463**Group Art Unit: 1631****Filed: April 13, 1999****Examiner: Marjorie A. Moran**

**Title: Identification Of Genetic Targets For Modulation By Oligonucleotides And
Generation Of Oligonucleotides For Gene Modulation**

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On 23 SEPTEMBER 2005


Paul K. Legaard, Reg. No. 38,534

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

REQUEST FOR RECONSIDERATION

In response to the Final Rejection dated May 23, 2005 in connection with the above-identified patent application, Applicants respectfully request reconsideration.

Claims 55, 56, 58-72, 74-76, 78-83, 85-87, and 99-102 are pending in the present application.

I. The Finality of the Office Action Is Premature

The Final Rejection asserts at page 2 that the because all the claims of the present application are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds of art of record in the next Office Action if they had been entered in the application prior to entry under 37 CFR 1.114, the present Action is made Final. Applicants, however, respectfully request that

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the finality of the Office Action be withdrawn because it is **premature**. M.P.E.P. 706.07(b) states, in part:

However, it **would not be proper** to make final a first Office action in a continuing or substitute application where that application contains material which was presented in the earlier application after final rejection or closing of prosecution but was **denied entry** because (A) **new issues were raised that required further consideration and/or search**, or (B) the issue of new matter was raised. (emphasis added)

In this regard, the Examiner's attention is drawn to the Advisory Action dated December 9, 2004 in which the proposed amendments of September 8, 2004 were **denied entry** because they "**raise new issues that would require further consideration and/or search**." Thus, the finality of the present first Office Action is premature. Accordingly, Applicants respectfully request that the finality be withdrawn.

II. The Claimed Invention Is Supported by Ample Written Description

Claims 55, 56, 58-72, 74-76, 78-83, 85-87, and 99-102 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants traverse the rejection and respectfully request reconsideration because the specification provides ample written description supporting the claimed inventions.

The Office Action asserts at page 3 that the step of generating oligonucleotide sequences is performed before any step of calculating thermodynamic properties or score, thus there is no support for generating an *in silico* compound of any kind according to a thermodynamic property, whether in combination with another property or alone. Applicants disagree.

Claim 55, for example, recites a method comprising:

generating *in silico* virtual compounds according to a thermodynamic property and at least one other criterion selected from targeting to functional regions of a target nucleic acid sequence, uniform distribution to said target nucleic acid sequence, and combinations thereof, wherein synthetic compounds corresponding to said virtual compounds modulate

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the expression of said target nucleic acid sequence; (emphasis added).

The apparent confusion between “generating oligonucleotide sequences” and “generating an *in silico* compound” recited in the Office Action appears to be at the crux of the rejection. It is quite true that one skilled in the art may generate oligonucleotide sequences prior to, for example, calculating thermodynamic properties, targeting to functional regions of a target nucleic acid sequence, or uniform distribution to the target nucleic acid sequence, and combinations thereof. This not does mean, however, that *in silico* compounds cannot be generated according to a thermodynamic property. It is upon carrying out such criterion recited in the claim that one skilled in the art can “generate *in silico* compounds” (as opposed to generating oligonucleotide sequences). Generating oligonucleotide sequences simply serves as a convenient starting point, for example, along with many other criteria, such as those recited in the claim, for generating *in silico* “compounds.” Indeed, steps 300 and 400, and desired criterion thereunder, can be carried out to generate an *in silico* “compounds” (see, for example, page 15, line 24 to page 32, line 3 of the specification). Thus, an end result to carrying out the criterion recited in the claim is the generation of “*in silico* virtual compounds” as recited in claim 55, for example. Thus, there is ample support in the specification for the recited claims.

The Office Action also asserts at page 3 that the assessment of a compound for a criterion such as hybridization (i.e., targeting) is “performed separately from the thermodynamic property calculations.” Again, Applicants disagree with the Examiner’s interpretation of the claims and specification.

Applicants teach at, for example, page 7, lines 5-18 of the specification:

The present invention is directed to iterative processes for defining chemical compounds with prescribed sets of physical, chemical and/or biological properties, and to systems for implementing these processes. During each iteration of a process as contemplated herein, a target nucleic acid sequence is provided or selected, and a library of (candidate) virtual compounds is generated *in silico* (that is in a computer manipulatable and reliable form) according to defined criteria. A library of virtual compounds is generated. These virtual compounds are reviewed and compounds predicted to have particular desired properties are selected.

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Thus, Applicants quite clearly teach that a library of virtual compounds is generated *in silico* according to defined criteria. Applicants expand upon the defined criteria in, for example, steps 300 and 400, and desired criterion thereunder (see, for example, page 15, line 24 to page 32, line 3 of the specification). Thus, for example, one skilled in the art may choose a thermodynamic property (as recited in claim 55, for example) as a desired criterion by which to generate *in silico* compounds. The skilled artisan may also further desire to take into consideration targeting to functional regions of a target nucleic acid sequence or uniform distribution to the target nucleic acid sequence as additional desired criterion, or both (i.e., a combination) (as recited in claim 55, for example). There is absolutely no requirement in either the claims or the specification to perform thermodynamic calculations "separately" from other criterion, although one skilled in the art may desire to do so. The specification quite clearly teaches the generation of *in silico* compounds, from which actual compounds can be generated. The specification also quite clearly provides numerous criterion which the skilled artisan can use in generating the *in silico* compounds. Indeed, any combination of these criterion can be used, and is up to the desires of the skilled artisan who is generating the *in silico* compounds. Thus, there is ample support in the specification for the recited claims.

In view of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. §112, first paragraph, as allegedly failing to provide sufficient written description be withdrawn.

III. The Claimed Invention Is Not Obvious

Claims 55, 56, 58-72, 74-76, 78-83, 85-87, and 99-102 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over the combination of the following references: 1) U.S. Patent No. 5,463,564 (hereinafter, the "Agrafiotis reference"), 2) Uhlmann et al., Chem. Rev., 1990, 90, 543-584 (hereinafter, the "Uhlmann reference"), 3) U.S. Patent No. 5,639,603 (hereinafter, the "Dower reference"), 4) U.S. Patent No. 5,720,923 (hereinafter, the "Haff reference"), and 5) U.S. Patent No. 5,650,122 (hereinafter, the "Harris reference"). The Office Action maintains that it would have been obvious to perform antisense drug design via the Agrafiotis and Uhlmann references, synthesize the compounds via the Dower reference, and perform assays via the Haff or Harris references. Applicants traverse the rejection and

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respectfully request reconsideration because the combination of the cited references fails to produce the claimed methods.

The Office Action asserts at page 5 that the Agrafiotis reference reports "analysis of physical and/or electronic property data related to his generated compounds" and that "his synthesis generator uses a combination of data including structural, electronic and physiochemical, and receptor fit criteria" and thus teaches using thermodynamic criteria with other criteria. The portions of the Agrafiotis reference relied upon in the Office Action, however, do not support this conclusion.

For example, column 11, lines 57-65 of the Agrafiotis reference report that the analysis robots may additionally include a physical and/or electronic property analysis module(s) which "analyzes the compounds synthesized by the Chemical Synthesis Robot" to obtain physical and/or electronic property data related to the compounds. Thus, this portion of the Agrafiotis reference relied upon in the Office Action supports the notion of obtaining physical and/or electronic property data related to the actual compounds already synthesized, and not to using thermodynamic criteria with other criteria to generate *in silico* compounds.

Column 12, lines 10-47 of the Agrafiotis reference report a reagent database 120 and a structure-activity database 122. These databases contain data regarding the reagents in the Reagent Repository as well as Structure-Activity data, respectively. The Structure-Activity data is obtained as a result of the analysis of the compounds performed by the analysis robots. Nowhere does this portion of the Agrafiotis reference teach using thermodynamic criteria with other criteria to generate *in silico* compounds. The fact that the databases reported in the Agrafiotis reference may be in a computer readable format does not mean that the compounds produced by using thermodynamic criteria with other criteria are also *in silico* compounds. Indeed, it appears that these two databases are used for the actual generation of real compounds.

Lastly, column 16, line 60 to column 17, line 2 reports that the Synthesis Protocol Generator 104 uses several parameters to generate an initial Directed Diversity Chemical Library, which is a library of real compounds. Nowhere does this portion of the Agrafiotis reference teach using thermodynamic criteria with other criteria to generate *in silico* compounds.

Applicants respectfully submit that the references, alone or in combination fail to teach or suggest the claimed methods, and more specifically, fail to teach or suggest the instantly

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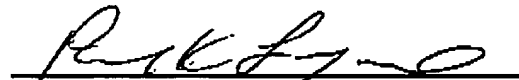
claimed combination of "a thermodynamic property with at least one other criterion selected from targeting to functional regions of a target nucleic acid sequence, uniform distribution to said target nucleic acid sequence, and combinations thereof."

Thus, the claimed invention is not obvious in view of the combination of cited references. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §103(a) be withdrawn.

IV. Conclusion

In view of the foregoing, Applicants respectfully submit that the claims are in condition for allowance. An early notice of the same is earnestly solicited. The Examiner is invited to contact Applicants' undersigned representative at (215) 665-6914 if there are any questions regarding Applicants' claimed invention.

Respectfully submitted,



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